CLINICAL STUDY PROTOCOL

Phase I/Ib trial of combined 5'azacitidine and carboplatin for recurrent/refractory pediatric brain and solid tumors

COZMOS: Phase I/Ib trial of COmbined epigenetic therapy with 5'-aZacitidine and carboplatin for recurrent/refractory paediatric brain and solid tuMOurs

Clinical Trial Protocol No:	Sponsor Protocol No. 1000055621 Ozmosis Study No. OZM-077
Protocol Version #:	3.1
Protocol Date:	07-Jul-2020
Phase of Study:	I/Ib
Sponsor:	Hospital for Sick Children
Sponsor Address:	555 University Ave. Toronto, ON M5G 1X8
Source of Agent:	Celgene Corporation

Protocol History

Revision:	Version #3.0; dated 21-Feb-2020
Revision:	Version #2.0; dated 21-Jun-2018
Revision:	Version #2.0; dated 17-May-2018
Revision:	Version #1.1; dated 30-Mar-2017
Revision:	Version #1.0; dated 20-Mar-2017
Revision:	Version #1.0; dated 23-Feb-2017
Original:	Version #1.0; dated 13-Dec-2016

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Sponsor's Agreement to Protocol Version#3.1 07-Jul-2020

Name of Authorized Personnel (Print) _____

Title of Authorized Personnel (Print) _____

Signature of Authorized Personnel: _____

Date of Approval: _____
DD-MMM-YYYY

SYNOPSIS

Study Title:	Phase I/Ib trial of combined 5'azacitidine and carboplatin for recurrent/refractory pediatric brain and solid tumors.
Primary Objectives:	Determine the safety and maximum tolerated dose of carboplatin when combined with 5-azacitidine.
Secondary Objectives:	The secondary objectives are: • Characterization of the pharmacodynamics of 5'-azacitidine in combination with carboplatin • Assessment of intratumoral DNA demethylation as a preliminary indication of efficacy of the combination • Assessment of disease response as a preliminary indication of efficacy of this combination against recurrent, refractory pediatric brain and solid tumors
Study Design:	This is a multi centre phase I/Ib study of combined 5'azacitidine and carboplatin for recurrent/refractory pediatric brain and solid tumors. The rolling 6 design will be utilized for dose escalation portion of the study.
Duration:	The enrollment period of the study is expected to be approximately 6 months for dose escalation phase and 1 year for dose expansion phase. The treatment period for an individual patient is expected to be 12 cycles (approximately 12 months). The follow up period is 18 months.
Planned Total Sample Size:	In the dose escalation phase of the study, up to 24 patients will be enrolled. In the expansion cohorts, up to 42 patients will be enrolled across 2 strata: **Stratum 1:** approximately 30 patients in recurrent ependymoma expansion cohort **Stratum 2:** approximately 12 patients in recurrent brain and solid tumour expansion cohort

Inclusion/Exclusion Criteria:	**Inclusions:** 1) Greater than the age of 1 year and under age 18 at the time of study enrolment 2) Recurrent or refractory brain or solid tumor, including recurrent or refractory ependymoma 3) Tissue from diagnosis or resection prior to registration must be available (either flash frozen tissue or an FFPE block) 4) Previous therapy with carboplatin will be permitted 5) Failed first line treatment (surgery, radiation therapy or chemotherapy) and should not be eligible for treatment with curative potential. 6) Be at least 4 weeks from the completion of myelosuppressive chemotherapy and/or biologic agents before starting day 1 of this study treatment 7) Be at least 14 days from the completion of radiation therapy and MIBG before starting day 1 of this study treatment 8) Be at least 3 months post hematopoetic stem cell rescue following myeloablative therapy before starting day 1 of this study treatment 9) Must have visible disease on imaging. Resection of visible disease is permitted while on study after two cycles including achievement of a gross total resection. If a resection is performed while on study, fresh frozen tissue should be submitted for analysis. 10) Concurrent medications will be limited to supportive medications/agents including but not limited to anti-emetics, steroids, analgesics and non-enzyme inducing anticonvulsants. Strong inducers of the P450 system will not be permitted. Other concurrent medications require approval of the study Sponsor. 11) Ability of the parent and/or child to understand and the willingness to sign a written informed consent document 12) Karnofsky ≥ 50 for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age (See Appendix I for the Karnofsky-Lansky Scores). Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score. Patients with posterior fossa syndrome/cerebellar mutism demonstrating clear

	improvement post-surgically can be enrolled based on physician discretion. 13) Adequate hepatic, renal, marrow and cardiac function as defined below within 28 days prior to cycle 1 day 1: • Serum creatinine within normal institutional limits or creatinine clearance greater than 60mL/min • Serum bilirubin <1.5 times upper limit of institutional normal. Higher levels are acceptable if these can be attributed to active hemolysis or ineffective erythropoiesis • AST, ALT and Alkaline Phosphatase <3 times upper limit of institutional normal. If liver metastases are present, then <5 times upper limit of normal is permitted. • Normal QTc interval at screening ECG (baseline echocardiogram is not required) • Adequate marrow function defined below within 14 days prior to cycle 1 day 1: o Leukocytes greater than or equal to 1000 $x10^6$/L o Absolute neutrophil count greater than or equal to 0.75 $x10^9$/L o Platelets greater than or equal to 75 $x10^9$/L o Hemoglobin greater than or equal to 10g/dL (may be transfused). **Exclusions:** 1) Female patient who is pregnant or breast feeding (Lactating females must agree not to breast feed while taking azacitidine) or with childbearing potential and not willing to use a double method of contraception up to 3 months after the end of study treatment. Male patient who is not willing to use a barrier method of contraception up to 6 months after the end of study treatment. 2) Patients may not be receiving any other investigational agents within 30 days prior to day 1 of protocol treatment 3) Prior therapy with a DNA demethylase inhibitor 4) Evidence of known preexisting cardiac toxicity (shortening fraction below 28%; shortening fraction measures and ratios the change in the diameter of

	the left ventricle between the contracted and relaxed states) 5) Abnormal coagulation parameters (PT >15 seconds, PTT>40 seconds, and/or INR >1.5) 6) Significant active cardiac disease within the previous 6 months including: - NYHA class 3 or 4 CHF - Unstable angina - Myocardial infarction 7) Known or suspected hypersensitivity to azacitidine or mannitol carboplatin 8) Previous carboplatin exposure is not an exclusion criteria but previous allergic reaction to carboplatin will exclude enrolment. 9) Patient must not require use of enzyme inducing anticonvulsants; patients who are receiving an enzyme inducing anticonvulsant must be able to switch to a non-enzyme inducing anticonvulsant such as Levitiracetam, Clobazam, Lacosamide or Topiramate at least 2 weeks prior to study enrolment. 10) Uncontrolled systemic fungal, bacterial or viral infection (defined as ongoing signs/symptoms related the infection without improvement despite appropriate antibiotics, antiviral therapy and/or other treatment) 11) Active viral infection with HIV or hepatitis type B or C 12) Patients with advanced malignant hepatic tumors
Screening Assessments:	• Written Informed Consent • Inclusion/Exclusion Criteria • Medical History • Physical Examination • Neurological Examination • Audiogram • Skin Exam (bedside) • Height and Weight • Performance Status • Vital Signs • Evaluation of the Tanner Stage • Evaluation of Menstrual Status (females only) • Serum Pregnancy Test (if pubertal female) • ECG • Hematology • Biochemistry

	• PT/INR and PTT • GFR • Tumour Assessment • Tumour Tissue Biopsy or Resection • Baseline Symptoms
Treatment and Post-Treatment Assessments:	<u>Treatment Phase</u> • Physical Examination • Neurological Examination • Audiogram • Skin Exam (bedside) • Height and Weight • Performance Status • Vital Signs • Hematology • Biochemistry • GFR • Tumour Assessment • Tumour Tissue Biopsy or Resection • Review of screening skin exam and audiogram • Pharmacodynamics Blood Sample Collection • AE Assessment • Concomitant Medications <u>End of Treatment Visit</u> • Physical Examination • Vital Signs • Tumour Assessment • AE Assessment • Concomitant Medications <u>Safety Visit (30 days after last dose)</u> • Physical Examination • Neurological Examination • Audiogram • Skin Exam (bedside) • Height and Weight • Performance Status • Vital Signs • Hematology • Biochemistry • AE Assessment

	• Concomitant Medications <u>Survival Follow Up (at 18 months after completion of study)</u> • Survival Status obtained from patient medical records or follow-up call
Pharmacodynamic Assessments:	Mandatory whole blood samples will be collected for characterization of the pharmacodynamics of 5'-azacitidine in combination with carboplatin. Tumour tissue (either flash frozen or FFPE) from diagnosis must be available for inclusion into this study. If clinically indicated, a biopsy/resection is permitted while on study however tissue should be submitted for analysis. Tumour tissue will be used to assess intratumoral DNA demethylation as a preliminary indication of efficacy of the drug combination. Refer to Study Calendar in section 4 and section 8.4.
Response:	Response criteria as per section 8 will be utilized for this study.
Safety Variables & Analysis:	This study will utilize the CTCAE Version 4.03 for adverse event reporting.
Statistical Analysis:	The following study populations are defined and will be analyzed as specified below. The population evaluable for safety will be the safety population. <u>The Intent to Treat (ITT) population:</u> the total population of patients registered in the study <u>Safety population:</u> all **registered** patients who received at least one dose of any study drug. <u>Efficacy population:</u> all enrolled patients who completed at least one cycle of study medication (both VIDAZA® and Carboplatin) and had evaluable tumour assessment Any patient who is registered on to this trial but never receives study treatment will be described, including the reason(s) for non-participation.

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Due to contractual obligations with the international sponsor we are unable to provide the full protocol document.

More information about the trial can be found on the Australian New Zealand Clinical Trials Registry (anzctr.org.au) under record number NCT03206021.

Please contact the office of the Australian and New Zealand Children's Haematology / Oncology Group (ANZCHOG) for further details. Email: info@anzchog.org

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